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1: Biochem Soc Trans. 2007 Jun;35(Pt 3):559-60.

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Transactions

The emerging role of serine proteases in apoptosis.

Moffitt KL, Martin SL, Walker B.

School of Pharmacy, Queen's University, Belfast BT9 7BL, Northern Ireland, UK.
kellylmoftt@hotmail.com

Unregulated apoptosis can be due to a disruption in the balance and control of both intra- and inter-cellular proteolytic activities leading to various disease states. Many proteases involved in apoptotic processes are yet to be identified; however, several are already well characterized. Caspases traditionally held the predominant role as prime mediators of execution. However, latterly, evidence has accumulated that non-caspases, including calpains, cathepsins, granzymes and the proteasome have roles in mediating and promoting cell death. Increasingly, research is implicating serine proteases within apoptotic processing, particularly in the generation of nuclear events such as condensation, fragmentation and DNA degradation observed in late-stage apoptosis. Serine proteases therefore are emerging as providing additional or alternative therapeutic targets.

Publication Types:

- Review

PMID: 17511651 [PubMed - indexed for MEDLINE]

2: Cell Cycle. 2007 Jan 15;6(2):136-8. Epub 2007 Jan 27.

Related Articles, Links



The calpain system as a modulator of stress/damage response.

Demarchi F, Schneider C.

Laboratorio Nazionale Consorzio Interuniversitario Biotecnologie, AREA Science Park, Trieste, Italy. demarchi@lncib.it

Ubiquitously expressed mu- and m-calpain proteases consist of 80-kDa catalytic subunits encoded by the Capn1 and Capn2 genes, respectively, and a common 28-kDa regulatory subunit encoded by the calpain small 1 (Capns1) gene. The mu- and m-calpain proteases have been implicated in both pro- or anti-apoptotic functions. We have found that Capns1 depletion is coupled to increased sensitivity to apoptosis triggered by a number of autophagy-inducing stimuli in mammalian cells. Therefore we investigated the involvement of calpains in autophagy using MEFs derived from Capns1 knockout mice and Capns1 depleted human cells as model systems. We found that autophagy is impaired in Capns1 deficient cells by immunostaining of the endogenous autophagosome marker LC3 and electron microscopy experiments. Accordingly, the enhancement of lysosomal activity and long-lived proteins degradation, normally occurring upon starvation, are also reduced. In Capns1 depleted cells ectopic LC3 accumulates in early endosome-like vesicles that might represent a salvage pathway for protein degradation when autophagy is defective. Calpain represents a promising target for cancer therapy since its activity is tightly linked to tumor progression. Indeed it is elevated during transformation, it is required for autophagy and survival of cancer cells and plays a key role in metastatic cell migration and angiogenesis.

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3: Drug Discov Today. 2006 Oct;11(19-20):917-23. Epub 2006 Sep 7. [Related Articles, Links](#)

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The therapeutic potential of the calpain family: new aspects.

Saez ME, Ramirez-Lorca R, Moron FJ, Ruiz A.

Department of Structural Genomics, Neocodex, Centro de Negocios Charles Darwin s/n, Isla de la Cartuja, 41092-Sevilla, Spain. mesaez@neocodex.es

The calpain family is a group of cysteine proteases unique in their dependency on calcium to attain functionally active forms. Calpains are involved in a wide range of cellular calcium-regulated functions, including signal transduction, cell proliferation and differentiation, and apoptosis. Moreover, altered calpain activity has been observed in several human diseases. Specific calpain inhibitors hold promise for the treatment of neuromuscular and neurodegenerative diseases in which calpains have been shown to be upregulated (e.g. Parkinson's disease and Duchenne muscular dystrophy). Conversely, calpain activators could be a useful approach for those diseases where reduced calpain activity has been observed, such as type 2 diabetes or metabolic syndrome.

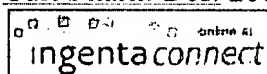
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Calpain inhibition: a therapeutic strategy targeting multiple disease states.

[Carragher NO.](#)

The Beaton Insititue for Cancer Research, Cancer Research UK, Glasgow G61 1BD, Scotland, UK. neil.carragher@astrazeneca.com

The calpains represent a well-conserved family of calcium-dependent cysteine proteases. They consist of several ubiquitous and tissue specific isoforms and exhibit broad substrate specificity influencing many aspects of cell physiology including migration, proliferation and apoptosis. Calpain activity in vivo is tightly regulated by its natural endogenous inhibitor calpastatin. Calpastatin specifically inhibits calpain and not other cysteine proteases by interaction with several sites on the calpain molecule. Inappropriate regulation of the calpain-calpastatin proteolytic system is associated with several important human pathological disorders including muscular dystrophy, cancer, Alzheimer's disease, neurological injury, ischaemia/reperfusion injury, atherosclerosis, diabetes and cataract formation. Recent advances in elucidating the tertiary structures of calpain 2 and its regulatory domain calpain 4, together with identification of new modes of regulating calpain activity provide new opportunities for the design of novel calpain inhibitors. Several classes of inhibitors, including peptidyl epoxide, aldehyde, and ketoamide inhibitors, targeting the active site have proven effective against the calpains and are in the process of evaluation in animal models of human disease. However, a major limitation to the clinical use of such inhibitors is their lack of specificity among cysteine proteases and other proteolytic enzymes. The development of a new class of calpain inhibitors that interact with domains outside of the catalytic site of calpain may provide greater specificity and therapeutic potential.

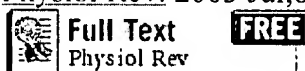
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▮ 5: [Physiol Rev.](#) 2003 Jul;83(3):731-801.

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The calpain system.

[Goll DE, Thompson VE, Li H, Wei W, Cong J.](#)

Muscle Biology Group, University of Arizona, Tucson, AZ 85721, USA.
darrel.goll@arizona.edu

The calpain system originally comprised three molecules: two Ca^{2+} -dependent proteases, mu-calpain and m-calpain, and a third polypeptide, calpastatin, whose only known function is to inhibit the two calpains. Both mu- and m-calpain are heterodimers containing an identical 28-kDa subunit and an 80-kDa subunit that shares 55-65% sequence homology between the two proteases. The crystallographic structure of m-calpain reveals six "domains" in the 80-kDa subunit: 1). a 19-amino acid NH_2 -terminal sequence; 2). and 3). two domains that constitute the active site, IIa and IIb; 4). domain III; 5). an 18-amino acid extended sequence linking domain III to domain IV; and 6). domain IV, which resembles the penta EF-hand family of polypeptides. The single calpastatin gene can produce eight or more calpastatin polypeptides ranging from 17 to 85 kDa by use of different promoters and alternative splicing events. The physiological significance of these different calpastatins is unclear, although all bind to three different places on the calpain molecule; binding to at least two of the sites is Ca^{2+} dependent. Since 1989, cDNA cloning has identified 12 additional mRNAs in mammals that encode polypeptides homologous to domains IIa and IIb of the 80-kDa subunit of mu- and m-calpain, and calpain-like mRNAs have been identified in other organisms. The molecules encoded by these mRNAs have not been isolated, so little is known about their properties. How calpain activity is regulated in cells is still unclear, but the calpains ostensibly participate in a variety of cellular processes including remodeling of cytoskeletal/membrane attachments, different signal transduction pathways, and apoptosis. Deregulated calpain activity following loss of Ca^{2+} homeostasis results in tissue damage in response to events such as myocardial infarcts, stroke, and brain trauma.

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▮ 6: [Curr Drug Targets CNS Neurol Disord](#). 2003 Jun;2(3):173-89. [Related Articles, Links](#)

Calpain and its involvement in the pathophysiology of CNS injuries and diseases: therapeutic potential of calpain inhibitors for prevention of neurodegeneration.

Ray SK, Banik NL.

Department of Neurology, Medical University of South Carolina, 96 Jonathan Lucas Street, Suite 309, P.O. Box 250606, Charleston, SC 29425, USA. raysk@musc.edu

Calpain is a Ca^{2+} -activated proteolytic enzyme involved in neurodegeneration in a variety of injuries and diseases of the central nervous system (CNS). Many calpain homologs have been discovered. Depending on the tissue distribution, calpains are broadly classified as ubiquitous and tissue-specific. Ubiquitous calpain isoforms, -

calpain and m-calpain, are abundantly expressed in the CNS. Calpastatin, an endogenous protein inhibitor, regulates the activity of ubiquitous calpain. Overactivation of calpain may degrade calpastatin, limiting its regulatory efficiency. Molecular structures of calpain and calpastatin have been deduced from cDNA cloning. The precise physiological function of calpain remains elusive. However, experimental evidence strongly suggests an important role for calpain in causing neurodegeneration in various injuries and diseases of the CNS. The increase in intracellular free Ca^{2+} levels in the course of injuries and diseases in the CNS causes overactivation of calpain, promoting degradation of key cytoskeletal and membrane proteins. Cleavage of these key proteins by calpain is an irreversible process that perturbs the integrity and stability of CNS cells, leading to programmed cell death or apoptosis. Calpain in conjunction with caspases can cause apoptosis of the CNS cells. An aberrant Ca^{2+} homeostasis inevitably activates calpain, which plays a crucial role in the pathophysiology of the CNS injuries and diseases. Therefore, calpain is a potential therapeutic target to prevent neurodegeneration. To this end, various cell-permeable calpain inhibitors have been synthesized for pharmacological inhibition of calpain activity. Some calpain inhibitors have shown significant neuroprotection in animal models of the CNS injuries and diseases, indicating their therapeutic potential.

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7: [Int J Biochem Cell Biol. 2002 Jul;34\(7\):722-5.](#)

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Calpain.

[Perrin BJ, Huttenlocher A.](#)

Cellular and Molecular Biology Graduate Program, University of Wisconsin, 1300 University Avenue, Madison, WI 53706, USA.

The calcium-dependent thiol proteases, calpains, are widely expressed with ubiquitous and tissue specific isoforms. Calpains have been implicated in basic cellular processes including cell proliferation, apoptosis and differentiation. The focus of the current review is to summarize recent findings implicating calpains in cytoskeletal rearrangements and cell migration. Calpain cleaves many cytosolic proteins and therefore to be effective and limited in its scope, calpain activity has to be tightly regulated both temporally and spatially. Some mechanisms of regulation include calcium, growth factor-mediated phosphorylation and membrane targeting. Calpain inhibition reduces migration rates and inhibits cell invasiveness. Two putative mechanisms of calpain action during migration include its role as a signaling intermediate, acting upstream of Rho, and its effects on focal adhesion structure and disassembly. Therefore, calpains and downstream signaling molecules may be future targets for therapeutic interventions to treat cancer or chronic inflammation.

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PMID: 11950589 [PubMed - indexed for MEDLINE]

▮ 8: [J Neurosci Res](#). 1999 Oct 1;58(1):167-90.[Related Articles, Links](#)**Caspase and calpain substrates: roles in synaptic plasticity and cell death.****[Chan SL](#), [Mattson MP](#).**

Sanders-Brown Research Center on Aging and Department of Anatomy and Neurobiology, University of Kentucky, Lexington 40536, USA.

Neurons are an unusual type of cell in that they send processes (axons and dendrites) over great distances. This elaborate morphology, together with their excitability, places neurons at risk for multiple insults. Recent studies have demonstrated that apoptotic and excitotoxic mechanisms not only contribute to neuronal death, but also to synaptic dysfunction and a breakdown in neural circuitry (see Mattson and Duan [1999] *J. Neurosci. Res.* 58:152-166, this issue). Proteases of the caspase and calpain families have been implicated in neurodegenerative processes, as their activation can be triggered by calcium influx and oxidative stress. Caspases and calpains are cysteine proteases that require proteolytic cleavage for activation. The substrates cleaved by caspases include cytoskeletal and associated proteins, kinases, members of the Bcl-2 family of apoptosis-related proteins, presenilins and amyloid precursor protein, and DNA-modulating enzymes. Calpain substrates include cytoskeletal and associated proteins, kinases and phosphatases, membrane receptors and transporters, and steroid receptors. Many of the substrates of caspases and calpains are localized in pre- and/or postsynaptic compartments of neurons. Emerging data suggest that, in addition to their roles in neurodegenerative processes, caspases and calpains play important roles in modulating synaptic plasticity. The present article provides a review of the properties of the different caspases and calpains, their roles in cell death pathways, and the substrates upon which they act. Emerging data are considered that suggest key roles for these proteases in the regulation of synaptic plasticity. Copyright 1999 Wiley-Liss, Inc.

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PMID: 10491581 [PubMed - indexed for MEDLINE]

▮ 9: [Biochem J](#). 1997 Dec 15;328 (Pt 3):721-32.[Related Articles, Links](#)**Structure and physiological function of calpains.**

Sorimachi H, Ishiura S, Suzuki K.

Laboratory of Molecular Structure and Function, Institute of Molecular and Cellular Biosciences, University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113, Japan.

For a long time now, two ubiquitously expressed mammalian calpain isoenzymes have been used to explore the structure and function of calpain. Although these two calpains, mu- and m-calpains, still attract intensive interest because of their unique characteristics, various distinct homologues to the protease domain of mu- and m-calpains have been identified in a variety of organisms. Some of these 'novel' calpain homologues are involved in important biological functions. For example, p94 (also called calpain 3), a mammalian calpain homologue predominantly expressed in skeletal muscle, is genetically proved to be responsible for limb-girdle muscular dystrophy type 2A. Tra-3, a calpain homologue in nematodes, is involved in the sex determination cascade during early development. PalB, a key gene product involved in the alkaline adaptation of *Aspergillus nidulans*, is the first example of a calpain homologue present in fungi. These findings indicate various important functional roles for intracellular proteases belonging to the calpain superfamily.

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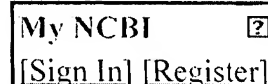
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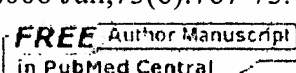
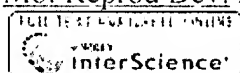
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Calpain 11 is unique to mouse spermatogenic cells.

Ben-Aharon I, Brown PR, Shalgi R, Eddy EM.

Department of Cell and Developmental Biology, Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel.

The calpains are a family of calcium-dependent thiol proteases involved in intracellular processing of proteins. They occur as heterodimers containing one of various large subunits and a common small subunit. Some of the large subunits are expressed ubiquitously and others are expressed in a restricted set of tissues. We have cloned the cDNA for mouse calpain 11 and demonstrated that it is expressed specifically in the mouse testis. The mRNA begins to accumulate in the testis between days 14 and 16 after birth, corresponding to the period of pachytene spermatocyte development. The protein is detected by day 18 after birth, during mid to late pachytene spermatocyte development, and is present in the acrosomal region of spermatozoa from the cauda epididymis. The expression of calpain 11 during spermatogenesis and its localization in spermatozoa suggest that it is involved in regulating calcium-dependent signal transduction events during meiosis and sperm functional processes.

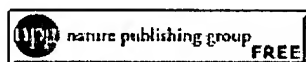
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☐ 2: [Cell Death Differ.](#) 2006 Nov;13(11):1927-37. Epub 2006 Mar 10.

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Caspase-independent death of meiotic and postmeiotic cells overexpressing p53: calpain involvement.

Coureuil M, Fouchet P, Prat M, Letallec B, Barroca V, Dos Santos C, Racine C, Allemand I.

Département de Radiobiologie et Radiopathologie (DRR), CEA/Institut Nationale de la Santé et de la Recherche Médicale Unité 566/Université Paris VII, 60 avenue du général Leclerc, BP6, Fontenay aux Roses Cedex 92265, France.

In a model of male sterility (MTp53) owing to enforced p53 expression in spermatocytes II and spermatids of transgenic mice, we focused on the role of caspases. Most of them are expressed in all differentiation stages, but only the transcriptional levels of caspase-2 and caspase-3 are modified in MTp53 germ cells. In normal testis, cleaved caspase-3 and caspase-9 are detected during the elongation of spermatids. Despite this constitutive presence of caspases during terminal differentiation, calpains are the main effectors of germ cell loss in MTp53 testes: calpain 1 RNA levels are increased, caspase-3-like activity is markedly decreased while calpain activity is higher and the calpain inhibitor E64d ((2S, 3S)-trans-epoxysuccinyl-L-leucylamido-3-methylbutane ethyl ester) reduces TUNEL labeling in MTp53 testis, whereas pancaspase inhibitor zVADfmk (N-benzyloxycarbonyl-Val-Ala-Asp(OMe)-fluoromethylketone) has no effect. Our work suggests that despite the presence, and potent involvement, of caspases in male haploid cell maturation, calpains are the executioners of the death of terminally differentiating germ cells.

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3: Arch Biochem Biophys. 2005 Aug 1;440(1):46-53.

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FULL-TEXT ARTICLE

Correlation between bovine calpastatin mRNA transcripts and protein isoforms.

Raynaud P, Gillard M, Parr T, Bardsley R, Amarger V, Levéziel H.

Unité de Génétique Moléculaire Animale, UMR 1061 INRA, Université de Limoges, Faculté des Sciences et Techniques, 123 av. Albert Thomas, 87060 Limoges Cedex, France.

Calpastatin is a specific calpain protease inhibitor: calpains are a family of calcium-activated neutral proteases, which have been implicated in various processes. Despite all the available data concerning calpastatin, little is known about how this gene is regulated, particularly in bovine. The existence of four types of transcripts differing at their 5' ends (Type I, II, III, and IV) has been demonstrated. Here, we show that the Type I, II, and III transcripts are ubiquitous while Type IV is testis-specific. In addition, a Northern blot analysis revealed that the Type III transcript may have three different 3' termini. Using specific anti-peptide anti-sera, a correspondence between a 145 and a 125 kDa isoforms, and Type I and/or II and III transcripts, respectively, has been established. Finally, we discuss the origin of a 70 kDa isoform, recognized by anti-sera

directed against the N-terminal region.

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▮ 4: [Gene](#). 2001 Aug 22;274(1-2):245-52.

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 **FULL-TEXT ARTICLE**

Identification and characterization of two novel calpain large subunit genes.

Dear TN, Boehm T.

Department of Developmental Immunology, Max-Planck Institute for Immunobiology,
Stuebeweg 51, D-79108 Freiburg, Germany. neil.dear@ingenium-ag.com

Calpains are a family of related proteins, some of which have been shown to function as calcium-dependent cysteine proteases. CAPN1 and CAPN2, the most well characterized calpains, consist of a large (80 kDa) and a small (30 kDa) subunit. In mammals, 11 different paralogous genes encoding calpain large subunits have been identified. We report the identification of two further genes, CAPN13 and CAPN14, potentially encoding calpain large subunits. Radiation hybrid mapping localized both genes within a region mapped to 2p21-2p22. The CAPN13 mRNA exhibits a restricted tissue distribution with low levels of expression detected only in human testis and lung while CAPN14 mRNA could not be detected in any of the 76 tissues examined. Examination of the human genome sequence in the public and private consortia databases did not detect any further members of this gene family. Thus, there would seem to be 13 large subunit calpain genes in the human genome. Phylogenetic analysis reveals that the putative calpain large subunit proteins can be divided into three major groups. The 13 human large subunit genes and the single small subunit gene are located in eight syntenic groups on chromosomes 1, 2, 3, 6, 11, 15, 19 and X.

PMID: 11675017 [PubMed - indexed for MEDLINE]

▮ 5: [Dev Growth Differ](#). 2001 Oct;43(5):563-71.

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XCL-2 is a novel m-type calpain and disrupts morphogenetic movements during embryogenesis in *Xenopus laevis*.

Cao Y, Zhao H, Grunz H.

Department of Zoophysiology, University of Essen, 45117 Essen, Germany.

We identified a novel cDNA, XCL-2, encoding an m-type calpain, a calcium-dependent intracellular protease. This protein has all characteristic structures and active sites of

canonical calpains. Zygotic transcription of the gene was first detected at stage 10. It is expressed exclusively in the ventral circumblastoporal collar and the mesoderm-free zone at the most anterior tip of neural fold in late gastrulae and neurulae. In later stages, expression is only found in cement gland and proctodeum. It is also expressed in a tissue-specific manner. In adult tissues, various levels of expression were detected in brain, eye, heart, intestine, kidney, lung, stomach and testis, but not in liver, muscle, nerve, ovary, skin and spleen. Overexpression of wild-type XCL-2 suggests that this gene is involved in gastrulation movement and convergent extension during gastrulation and neurulation. Overexpression of a dominant-negative mutant caused a phenotype morphologically similar to, but histologically different from, that caused by overexpression of wild-type XCL-2. The mutant phenotype can be rescued by injection of wild-type XCL-2. These data suggest that XCL-2 plays an important role in convergent extension movements during embryogenesis in *Xenopus laevis*.

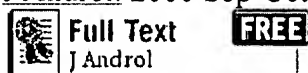
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6: J Androl. 2000 Sep-Oct;21(5):721-9.

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Calpain and calpastatin are located between the plasma membrane and outer acrosomal membrane of cynomolgus macaque spermatozoa.

Yudin AI, Goldberg E, Robertson KR, Overstreet JW.

Department of Obstetrics and Gynecology, University of California, Davis, USA.

Mammalian sperm must undergo an acrosome reaction prior to penetration of the zona pellucida and subsequent fusion with an oocyte. Sperm gain the capability to acrosome react after a period of capacitation, which primarily involves biochemical changes in the sperm membranes. The morphological events of the acrosome reaction have been well-documented, but the underlying cellular mechanisms that regulate capacitation and the acrosome reaction remain unclear. Antibodies to the 2 ubiquitous calpains, mu and m, as well as the small subunit, which associates with both calpains, were localized at the ultrastructural level to the region between the plasma membrane and the outer acrosomal membrane of cynomolgus macaque sperm. After the acrosome reaction, all of the anti-calpain antibodies labeled the acrosomal shroud, suggesting that calpains are located throughout the cytoplasmic area between the 2 outer sperm membranes. Calpastatin is an endogenous modulator of calpain activity and is also localized within the same cytoplasmic region as calpains. The antibodies used for ultrastructural localization were also used to probe Western blots of sperm extracts. Antibodies to either the mu- or m-calpain recognized an 80-kd protein, which is similar to the molecular weights of other ubiquitous calpains described. The small subunit (30 kd) was also recognized with a specific monoclonal antibody. An antibody to calpastatin recognized a major band at 78 kd and a lighter band at 45 kd, while the antibody to the testis-specific isoform of calpastatin (TCAST) recognized a 110-kd protein. We hypothesize that this cysteine protease system may be functional in cynomolgus

macaque sperm during capacitation, the acrosome reaction, or both.

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▮ 7: [Mech Dev.](#) 1999 Dec;89(1-2):201-9.

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Diverse mRNA expression patterns of the mouse calpain genes Capn5, Capn6 and Capn11 during development.

[Dear TN, Boehm T.](#)

Max-Planck Institute for Immunobiology, Stuebeweg 51, D-79108, Freiburg, Germany.
dear@immunbio.mpg.de

Calpains are a family of related proteins, originally classified on the basis of their calcium dependence and protease activity. Here we report the mRNA expression patterns during mouse development of the recently identified Capn5, Capn6 and Capn11 genes. The major expression sites of Capn5 during embryogenesis are the developing thymus, sympathetic and dorsal root ganglia. Capn6 mRNA is exclusively expressed during embryogenesis predominantly in developing skeletal and heart muscle overlapping closely with Capn3 expression domains. Expression was also observed in specific cells of the lung, kidney and placenta and in various epithelial cell types where the Capn6 mRNA appeared to be localized within the cell to the basal and apical ends. Capn11 mRNA is restricted exclusively to spermatocytes and only during the later stages of meiosis.

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▮ 8: [Genomics.](#) 1999 Jul 15;59(2):243-7.

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CAPN11: A calpain with high mRNA levels in testis and located on chromosome 6.

[Dear TN, Möller A, Boehm T.](#)

Max-Planck Institute for Immunobiology, Stuebeweg 51, Freiburg, D-79108, Germany.
dear@immunbio.mpg.de

Calpains are a superfamily of related proteins, some of which have been shown to

function as calcium-dependent cysteine proteases. In mammals, eight different calpains have been identified. We report the identification of a new mammalian calpain gene, CAPN11. The predicted protein possesses the features typical of calpains including potential protease and calcium-binding domains. The CAPN11 mRNA exhibits a highly restricted tissue distribution with highest levels present in testis. Radiation hybrid mapping localized the gene to human chromosome 6, within a region mapped to p12. Phylogenetic analysis suggests that, in mammals, the predicted CAPN11 protein is most closely related to CAPN1 and CAPN2. However, of the calpain sequences available, the predicted CAPN11 sequence exhibits greatest homology to the chicken micro/m calpain. Thus CAPN11 may be the human orthologue of micro/m calpain. The discovery of this new calpain emphasizes the complexity of the calpain family, with members being distinguished on the basis of protease activity, calcium dependence, and tissue expression. Copyright 1999 Academic Press.

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9: Genomics. 1997 Oct 1;45(1):175-84.

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FULLTEXT ARTICLE

A new subfamily of vertebrate calpains lacking a calmodulin-like domain: implications for calpain regulation and evolution.

Dear N, Matena K, Vingron M, Boehm T.

German Cancer Research Center, Heidelberg, Germany.

Calpains are calcium-dependent intracellular nonlysosomal proteases that are believed to participate in signal transduction. In vertebrates, five different calpains have so far been identified, of which three, mu-, m-, and mu/m-calpain, are ubiquitously expressed while the other two, nCL-1 (p94) and nCL-2, exhibit a restricted tissue distribution. We have identified two new vertebrate calpain genes, Capn5 and Capn6. The human and mouse amino acid sequences of these new calpains are the most divergent of the vertebrate calpains identified. They possess most of the residues conserved in calpain family members but the C-terminal region lacks any homology to the calmodulin-like domain of other vertebrate calpains. They both exhibit significant homology over the entire coding region to the protein encoded by the gene tra-3, involved in nematode sex determination, and Capn5 may represent its vertebrate orthologue. The predicted Capn6 protein lacks critical active site residues and may not be proteolytically active. Both genes are differentially expressed in human tissues with highest RNA levels for Capn5 occurring in the testis, liver, trachea, colon, and kidney, while Capn6 is highly expressed only in the placenta sample of the 50 tissues examined. Phylogenetic analysis suggests that the vertebrate calpains arose through a series of gene duplication events that began before the initial divergence of the vertebrate and invertebrate lineages. The discovery of these two new calpains highlights a hitherto unknown complexity of the calpain family with subclasses perhaps possessing different modes of regulation.

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